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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,721	12/14/2001	Jeanette McCarthy	MMI-003	5317
959	7590	05/04/2005	EXAMINER	
LAHIVE & COCKFIELD, LLP. 28 STATE STREET BOSTON, MA 02109			SMITH, CAROLYN L	
			ART UNIT	PAPER NUMBER
			1631	

DATE MAILED: 05/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/017,721	Applicant(s) MCCARTHY ET AL	
	Examiner Carolyn L Smith	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 October 2004 and 28 February 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 8-12, 41-43, 50-62 and 135-146 is/are pending in the application.
- 4a) Of the above claim(s) 41-43, 50-62, 135 and 144-146 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8-12 and 136-143 is/are rejected.
- 7) ☒ Claim(s) 8-12 and 136-143 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>08132004</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Applicant's amendments and remarks, filed 10/21/04 and 2/28/05, are acknowledged. Amended claims 8, 41, 42, 50-51 53, 56, and 58 and new claims 135-146 are acknowledged.

Applicant's arguments, filed 10/21/04 and 2/28/05, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from the previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 8-12 and 136-143 are herein under examination. Claims 41-43, 50-62, and 135 are withdrawn as they contain non-elected subject matter containing non-elected sets of nucleotide positions. Claims 144-146 are withdrawn as being drawn to methods of non-elected subject matter.

Applicants state in the Remarks section, filed 2/28/05, that they traverse the requirement of electing a sequence and an elected set of nucleotide positions. It is noted that the restriction is still deemed proper and was made FINAL in the previous office action, mailed 3/15/04. Applicants submit that there is no requirement that all of the elected species be set forth in one claim. This statement is found unpersuasive as it is noted that the election was not a species election, but rather a sequence election.

In the Remarks section, filed 10/21/04, Applicants request clarification of the withdrawn claims 49-62 which were drawn to non-elected species. It is noted that the Examiner made an inadvertent error referring to the nucleotide positions other than the elected set as non-elected

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species. In truth, the elected set of nucleotide positions is actually part of the sequence election requirement which is a restriction requirement and not a specie election requirement (see bottom of page 5 of restriction paper, mailed 6/19/03). The Examiner regrets the error and any confusion resulting therefrom.

Claim Objections

Claims 8-12 and 136-143 are objected to due to the inclusion of subject matter that has been non-elected due to restriction requirement and therefore withdrawn from consideration. Claims 9-12 are also rejected due to their direct or indirect dependency from claim 8. The non-elected subject matter is summarized as follows: Claim 8 recites the phrase “/or” on line 4 which refers to sets of nucleotide positions other than the elected set of nucleotide positions 55322, 53502, 60793, 58445, 52861, and 49556 of SEQ ID NO: 1. Claims 136-143 recite “41, 51, 56, 58, or 135” which refer to withdrawn claims. Correction is suggested by amending the claims to recite only the subject matter that is part of the elected instant invention.

Claim 136 is objected to because of the following informality: It recites an abbreviation, THBS1. Correction is suggested by amending in the full name in parentheses.

These objections are necessitated by amendment.

Claim Rejections – 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

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with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of the skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

LACK OF ENABLEMENT

Claims 8-12 and 136-143 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the claimed invention.

This rejection is maintained for claims 8-12 and necessitated by amendment for claims 136-143.

Applicants set forth six single nucleotide polymorphisms (SNPs) for thrombospondin 1 (THBS1), including one (G334u4 at nucleotide position 55322) which is a variant allele shown to be associated with increased risk for vascular disease (page 88, lines 6-7 of specification). The specification notes that all six SNPs in the THBS1 gene were found to be in linkage

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disequilibrium with each other and that five SNPs (nucleotide positions 53502, 60793, 58445, 52861, and 49556) can act as markers for G334u4 (page 88, first paragraph). Table 2 (page 88) notes that G334a16 (at nucleotide position 52861) and G334k2 (at nucleotide position 49556) are found in negative linkage disequilibrium meaning that subjects with these variant alleles are less likely to vascular disease. The methods in the instant invention are directed to a determination of the identity of all six nucleotides in these SNP locations; however, it does not appear that one of skill in the art would know, for example in claim 8, which variant alleles need to be present or which combinations of these variant alleles are necessary in order for the identification of a subject who is a candidate for further diagnostic evaluation for a vascular disease or disorder. For example, if the variant allele for G334u4 (positive indicator of vascular disease) is present as well as the variant alleles of G334a16 and G334k2 (negative indicators of vascular disease which are SNPs with negative linkage disequilibrium with G334u4), does this provide a stronger case for having coronary artery disease or not? Due to the necessity of additional undue experimentation, the lack of guidance and working examples addressing this issue, the instant claims are rejected due to a lack of enablement.

Applicants state they set forth which nucleotides are associated with an increased or decreased risk for vascular disease or indicate a subject as a candidate for further diagnostic evaluation. While the presence of only SNPs indicating a positive indication of vascular disease may confirm disease presence or while the presence of only SNPs indicating a negative indication of vascular disease may confirm a lesser likelihood of vascular disease, one skilled in the art would not know how to analyze other combinations of SNPs, such as the presence of negative and positive indicators in the same sample. Applicants state they have amended claim 8

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comprising the identity of nucleotide positions 55322, 53502, 60793, and/or 58445 or the full complement, wherein variant allele presence identifies candidate subjects for further diagnostic evaluation for a vascular disease or disorder. This statement is found unpersuasive as claim 8 contains two more nucleotide positions (to include the entire elected set of nucleotide positions) besides those mentioned above which also indicate a less likelihood of having a vascular disease (see specification, page 12, lines 12-19). Applicants mention new claim 135. It is noted that this claim is withdrawn as being drawn to non-elected subject matter. Applicants mention amended claim 41. It is noted that this claim is withdrawn as being drawn to non-elected subject matter. Applicants' arguments are found unpersuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-12 and 136-143 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These rejections are necessitated by amendment.

Claim 8, line 12, recites the phrase "at least one variant allele" which is vague and indefinite. It is unclear if this phrase is referring to a variant allele of SEQ ID NO: 1, a variant allele of SEQ ID NO: 1 involving the set of elected nucleotide positions, or a variant allele of

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any nucleotide sequence. Clarification of this issue via clearer claim wording is requested.

Claims 9-12 and 136-143 are also rejected due to their dependency from claim 8.

Claim 8, lines 12-13, recites the phrase “or the full complement thereof” which is vague and indefinite. It is unclear if this phrase is referring to the full complement of SEQ ID NO: 1 or of at least one variant allele. Clarification of this issue via clearer claim wording is requested.

Claims 9-12 and 136-143 are also rejected due to their dependency from claim 8.

Claim 8 recites the limitation “the reference allele at one or more of these positions” in the last two lines. There is insufficient antecedent basis for this limitation in the claim, because there is no prior mention of a reference allele. Clarification of this issue via clearer claim wording is requested. Claims 9-12 and 136-143 are also rejected due to their dependency from claim 8.

Claim 136 recites the limitation “THBS1” which is unclear as to whether the THBS1 is referring to a gene, gene fragment, mRNA, polypeptide, or various other possible scenarios. Correction of this issue via clearer claim wording is requested.

Claim 137 recites the limitation “the nucleotide sequence” in lines 2-3. There is insufficient antecedent basis for this limitation in the claim, as it is unclear if this phrase is referring to SEQ ID NO: 1, a generic variant allele, or the full complement of SEQ ID NO: 1 or a generic variant allele from instant claim 8. Clarification of this issue via clearer claim wording is requested.

Conclusion

No claim is allowed.

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Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The Central Fax Center number for official correspondence is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-0722.

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Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (571) 272-0549.

April 28, 2005

MARJORIE A. MORAN
PRIMARY EXAMINER

Marjorie A. Moran

5/2/05